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Respiratory Health Effects of Passive Smoking:

Review Draft

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Lung Cancer and Other Disorders

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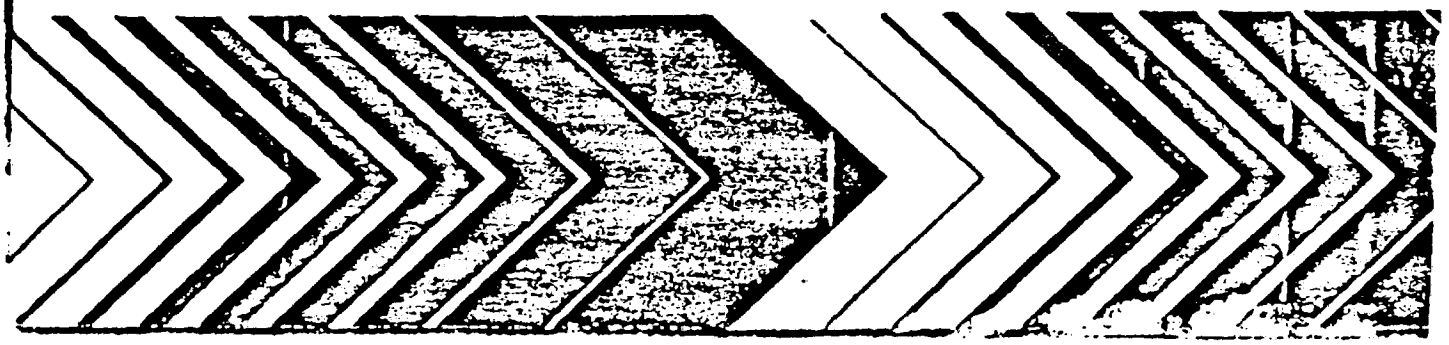
APPENDIX A



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SAB Review Draft

RESPIRATORY HEALTH EFFECTS OF PASSIVE SMOKING: LUNG CANCER AND OTHER DISORDERS

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PREFACE

This assessment of the respiratory health effects associated with passive smoking has been prepared by the Human Health Assessment Group, Office of Health and Environmental Assessment, Office of Research and Development, which is responsible for its scientific accuracy and conclusions. The assessment was prepared at the request of the Indoor Air Division, Office of Atmospheric and Indoor Air Programs, Office of Air and Radiation, which defined its scope and provided funding.

The document has been developed under the authority of Title IV of Superfund (The Radon Gas and Indoor Air Quality Research Act of 1986) to provide information and guidance on the potential hazards of indoor air pollutants.

An earlier draft of this document was made available for public review and comments in June 1990, and was reviewed by the Agency's Science Advisory Board in December 1990. This revision reflects the comments received from those reviews, plus additional comments from an internal review conducted in February and March 1992.

A comprehensive search of the scientific literature for this revision is complete through September 1991. In addition, a few studies published since then have been included in response to recommendations made by reviewers.

Due to both resource and time constraints, the scope of this report has been limited to an analysis of respiratory effects, primarily lung cancer in nonsmoking adults and noncancer respiratory illnesses in children, with emphasis on the epidemiologic data. Further, because two thorough reviews on passive smoking were completed in 1986 (by the U.S. Surgeon General and the National Research Council), this document provides a summary of those reports with a more comprehensive analysis of the literature appearing subsequent to those reports and an integration of the results.

It is the Agency's intention with the release of this draft to seek additional advice from its Science Advisory Board in preparation for release of a final report later this year.

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AUTHORS, CONTRIBUTORS, AND REVIEWERS

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Other OHEA staff responsible for the scientific content of sections of this document are Aparna M. Koppikar[1] and Jennifer Jinot[1]. Jennifer Jinot also served as a contributor and technical editor for a major portion of this report.

AUTHORS

Major portions of this revised report were prepared by ICF Incorporated, Fairfax, Virginia, under EPA Contract No. 68-00-0102. A list of authors follows:

Chapter 1:	Steven P. Bayard[1]
Chapter 2:	Jennifer Jinot[1]
Chapter 3:	Brian P. Leaderer[2]
Chapter 4:	Jennifer Jinot
Chapters 5/6:	Kenneth G. Brown[3]

---

[1]Human Health Assessment Group, Office of Health and Environmental Assessment, U.S. EPA, Washington, DC 20460.

[2]J. P. Pierce Foundation Laboratory, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, CT 06520. Subcontractor to ICF Inc.

[3]Kenneth G. Brown, Inc., P. O. Box 16608, Chapel Hill, NC 27516. Subcontractor to ICF Inc.

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Chapters 7:	Fernando D. Martinez[4]
Chapters 8:	Fernando D. Martinez and Steven P. Bayard
Appendix A:	Kenneth G. Brown, Neal R. Simonsen[3], and A. Judson Wells[3]
Appendix B:	A. Judson Wells
Appendix C:	Kenneth G. Brown
Appendix D:	Kenneth G. Brown and Neal R. Simonsen
Appendix E:	Kenneth G. Brown

CONTRIBUTORS

Numerous persons have provided helpful discussions or responded to requests for pre-prints, data, and other material relevant to this report. The authors are grateful to W.J. Blot, N. Britten, R.C. Brownson, P.A. Buffler, T.L. Butler, D.B. Coultas, K.M. Cummings, J. Fleiss, E.T.H. Fontham, Y.T. Gao, L. Garfinkel, S. Glantz, N.J. Haley, T. Hirayama, D.J. Hole, C. Humble, G.C. Kabat, J.C. Kleinman, L.C. Koo, M. Layard, P.N. Lee, M.D. Lebowitz, P. Macaskill, G.J. Knight, G.E. Palomaki, J.P. Pierce, J. Repace, H. Shimizu, W.F. Stewart, D. Trichopoulos, A. Wu-Williams, and R.W. Wilson.

[3]Kenneth G. Brown, Inc., P. O. Box 16608, Chapel Hill, NC 27516. Subcontractor to ICF Inc.

[4]Division of Respiratory Sciences, University of Arizona Medical Center, Tucson, AZ 85724. Subcontractor to ICF Inc.

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REVIEWERS

This document is a revision of an earlier External Review Draft (EPA/600/6-90/006A) that was released for public review and comment on June 25, 1990. The draft document subsequently was reviewed by the EPA Science Advisory Board (SAB) on December 4 and 5, 1990. Many of the revisions follow closely the valuable advice presented in the SAB's April 19, 1991, report to the Agency. Other revisions are based on comments received from peer reviewers and the public. In addition, many reviewers both within and outside the Agency provided assistance at various internal review stages.

The following members of the SAB's Indoor Air Quality and Total Human Exposure Committee (IAQTHEC) participated in the review of the External Review Draft.

Chairman

Dr. Morton Lippmann, Professor, Institute of Environmental Medicine, New York University Medical Center, Tuxedo, NY 10987

Vice Chairman

Dr. Jan A.J. Stolwijk, Professor, School of Medicine, Department of Epidemiology and Public Health, Yale University, 60 College Street, New Haven, CT 06510

Members of the IAQTHEC

Dr. Joan Daisey, Senioor Scientist, Indoor Environment Program, Lawrence Berkeley Laboratory, One Cyclotron Road, Berkeley, CA 94720

Dr. Victor G. Laties, Professor of Toxicology, Environmental Health Science Center-Box EHSC, University of Rochester School of Medicine, Rochester, NY 14642

Dr. Jonathan M. Samet, Professor of Medicine, Department of Medicine, The Univeristy of New Mexico School of Medicine, and The New Mexico Tumor Registry, 900 Camino De Salud, NE, Albuquerque, NM 87131

Dr. Jerome J. Wesolowski, Chief, Air and Industrial Hygiene Laboratory, California Department of Health, Berkeley, CA 94704

Dr. James E. Woods, Jr., Professor of Building Construction, College of Architecture and Urban Studies, 117 Burress Hall, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061-0156

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Consultants to the IAQTHEC

Dr. Neal L. Benowitz, Professor of Medicine, Chief, Division of Clinical Pharmacology and Experimental Therapeutics, University of California, San Francisco, Building 30, Fifth Floor, San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, CA 94110

Dr. William J. Blot, National Cancer Institute, 9000 Rockville Pike, Bethesda, MD 20892 (Federal Liaison to the Committee)

Dr. David Burns, Associate Professor of Medicine, Department of Medicine, University of California, San Diego Medical Center, 225 Dickenson Street, San Diego, CA 92103-1990

Dr. Delbert Eatough, Professor of Chemistry, Brigham Young University, Provo, UT 84602

Dr. S. Katharine Hammond, Associate Professor, Environmental Health Sciences Program, Department of Family and Community Medicine, University of Massachusetts Medical School, 55 Lake Avenue, North, Worcester, MA 06155

Dr. Geoffrey Kabat, Senior Epidemiologist, American Health Foundation, 320 East 43rd Street, New York, NY 10017

Dr. Michael D. Lebowitz, Professor of Internal Medicine, University of Arizona College of Medicine, Division of Respiratory Sciences, Tucson, AZ 85724

Dr. Howard Rockette, Professor of Biostatistics, School of Public Health, 318 Parran Hall, University of Pittsburgh, Pittsburgh, PA 15261

Dr. Scott T. Weiss, Channing Laboratory, Harvard University School of Medicine, Boston, MA 02115

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1. SUMMARY AND CONCLUSIONS

1.1. BACKGROUND

Tobacco smoking has long been recognized (e.g., U.S. DHEW, 1964) as a major cause of mortality and morbidity, responsible for an estimated 434,000 deaths per year in the United States (CDC, 1991a). Tobacco use is known to cause cancer at various sites, in particular the lung (U.S. DHHS, 1982; IARC, 1986). Smoking can also cause respiratory diseases (U.S. DHHS, 1984, 1989) and is a major risk factor for heart disease (U.S. DHHS, 1983). In recent years there has been concern that nonsmokers may also be at risk for some of these health effects as a result of their exposure ("passive smoking") to the tobacco smoke that occurs in various environments occupied by smokers. Although this environmental tobacco smoke (ETS) is dilute compared to the mainstream smoke (MS) inhaled by active smokers, it is chemically similar, containing many of the same carcinogenic and toxic agents.

In 1986, the National Research Council (NRC) and the Surgeon General of the U.S. Public Health Service independently assessed the health effects of exposure to ETS (NRC, 1986; U.S. DHHS, 1986). Both of the 1986 reports conclude that ETS can cause lung cancer in adult nonsmokers and that children of parents who smoke have increased frequency of respiratory symptoms and acute lower respiratory tract infections, as well as evidence of reduced lung function.

More recent epidemiologic studies of the potential associations between ETS and lung cancer in nonsmoking adults and between ETS and noncancer respiratory effects more than double the size of the database available for analysis from that of the 1986 reports. This U.S. EPA document critically reviews the current database on the respiratory health effects of passive smoking, and these data are utilized to develop a hazard identification for ETS and to make quantitative estimates of the public health impacts of ETS for lung cancer and various other respiratory diseases.

The weight-of-evidence analysis for the lung cancer hazard identification is developed in accordance with U.S. EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a) and established principles for evaluating epidemiologic studies. The analysis considers animal bioassays and genotoxicity studies, as well as biological measurements of human uptake of tobacco smoke components and epidemiologic data on active and passive smoking. The availability of abundant and consistent human data, and especially human data at actual environmental levels of exposure to the specific agent (mixture) of concern, allow a hazard identification to be made with

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a high degree of certainty. The conclusive evidence of the dose-related lung carcinogenicity of MS in active smokers (Chapter 4), coupled with information on the chemical similarities of MS and ETS and evidence of ETS uptake in nonsmokers (Chapter 3), is sufficient by itself to establish ETS as a known human lung carcinogen, or "Group A" carcinogen under U.S. EPA's carcinogen classification system. In addition, this document concludes that the overall results of 30 epidemiologic studies on lung cancer and passive smoking (Chapter 3), using spousal smoking as a surrogate of ETS exposure for female never-smokers, similarly justify a Group A classification.

The weight-of-evidence analyses for the noncancer respiratory effects are based primarily on a review of epidemiologic studies (Chapter 7). Most of the endpoints examined are respiratory disorders in children, where parental smoking is used as a surrogate of ETS exposure. For the noncancer respiratory effects in nonsmoking adults, most studies used spousal smoking as an exposure surrogate. A causal association was concluded to exist for a number of respiratory disorders where there was sufficient consistent evidence for a biologically-plausible association with ETS that could not be explained by bias, confounding, or chance. The fact that the database consists of human evidence from actual environmental exposure levels gives a high degree of confidence in this conclusion. Where there was suggestive but inconclusive evidence of causality, as was the case for asthma induction in children, ETS was concluded to be a risk factor for that endpoint. Where data were inconsistent or inadequate for evaluation of an association, as for acute upper respiratory tract infections and acute middle ear infections in children, no conclusions were drawn.

This report has also attempted to provide estimates of the extent of the public health impact, where appropriate, in terms of numbers of ETS-attributable cases in nonsmoking subpopulations. Unlike for qualitative hazard identification assessments where information from many sources adds to the confidence in a weight-of-evidence conclusion, for quantitative risk assessments the usefulness of studies usually depends on how closely the study population resembles nonsmoking segments of the general population. For lung cancer estimates among U.S. nonsmokers, the substantial epidemiology database of ETS and lung cancer among U.S. female never-smokers was considered to provide the most appropriate information. From the large number of similarly designed studies, pooled relative risk estimates were calculated and used in the derivation of the population risk estimates. The large number of studies available, the generally consistent results, and the condition of actual environmental levels of exposure increase the confidence in these estimates. Even with these conditions, however, uncertainties remain, such as in the use of questionnaires and current biomarker measurements to estimate past

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exposure, assumptions of exposure-response linearity, and extrapolation to male never-smokers and to exsmokers. Still, given the strength of the evidence for the lung carcinogenicity of tobacco smoke and the extensive human database from actual environmental exposure levels, fewer assumptions are necessary than is usual in U.S. EPA quantitative risk assessments and confidence in these estimates is rated medium to high.

Population estimates of ETS health impacts are also made for certain noncancer respiratory endpoints in children, specifically lower respiratory tract infections (LRIs, i.e. pneumonia, bronchitis, and bronchiolitis) and episodes and severity of attacks of asthma. Estimates of ETS-attributable cases of LRI in infants and young children are thought to have a high degree of confidence because of the consistent study findings and the appropriateness of parental smoking as a surrogate measure of exposure in very young children. Estimates of the number of asthmatic children whose condition is aggravated by exposure to ETS are less certain than those for LRIs because of different measures of outcome in various studies and because of increased extraparental exposure to ETS in older children. Estimates of the number of new cases of asthma in previously asymptomatic children also have less confidence because at this time the weight-of-evidence for asthma induction, while suggestive of a causal association, is not conclusive.

Most of the ETS population impact estimates are presented in terms of ranges, which are thought to reflect reasonable assumptions about the estimates of parameters and variables required for the extrapolation models. The validity of the ranges is also dependent on the appropriateness of the extrapolation models themselves.

While this report focuses only on the respiratory health effects of passive smoking, there may also be other health effects of concern. Recent analyses of more than a dozen epidemiology and toxicology studies (Steenland, 1992; NIOSH, 1991) suggest that ETS exposure may be a risk factor for cardiovascular disease. In addition, there were a few studies in the literature linking ETS exposure to cancers of others sites; at this time, that database appears inadequate for any conclusion. This report does not develop an analysis of either the nonrespiratory cancer or the heart disease data and takes no position on whether ETS is a risk factor for these diseases. If it is, the total public health impact from ETS will be greater than that discussed here.

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1.2. PRIMARY FINDINGS

A. Lung Cancer in Nonsmoking Adults

1. Passive smoking is causally associated with lung cancer in adults, and ETS, by the total weight-of-evidence, belongs in the category of compounds classified by EPA as Group A (known human) carcinogens.
2. An estimated range of 2,500 to 3,300 lung cancer deaths per year among nonsmokers (never-smokers and former smokers) of both sexes are attributable to ETS in the United States. The confidence in this range is medium to high with approximately 3,000 annual lung cancer deaths representing the best estimate.

B. Noncancer Respiratory Diseases and Disorders

1. Exposure of children to ETS from parental smoking is causally associated with:
   a. increased prevalence of respiratory symptoms of irritation (cough, sputum, and wheeze),
   b. increased prevalence of middle ear effusion (a sign of middle ear disease), and
   c. a small but statistically significant reduction in lung function as tested by objective measures of lung capacity.
2. ETS exposure of young children and particularly infants from parental (and especially mother's) smoking is causally associated with an increased risk of lower respiratory tract infections (pneumonia, bronchitis, and bronchiolitis). This report estimates that exposure to ETS contributes 150,000 to 300,000 lower respiratory tract infections annually in infants and children less than 18 months of age, resulting in 7,500 to 15,000 hospitalizations. These higher risks continue at a decreasing rate for children until about age 3, but no estimates are derived for children over 18 months.
3. a. Exposure to ETS is causally associated with additional episodes and increased severity of asthma in children who already have the disease. This report estimates that ETS exposure exacerbates symptoms in approximately 20% of this country's 2 million to 5 million asthmatic children and is a major aggravating factor in approximately 10%.

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b. In addition, the epidemiologic evidence is suggestive but not conclusive that ETS exposure increases the number of new cases of asthma in children who have not previously exhibited symptoms. Based on this evidence and the known ETS effects on both the immune system and lungs (e.g. atopy and airway hyperresponsiveness), this report concludes that ETS is a risk factor for the induction of asthma in previously asymptomatic children. Data suggest that relatively high levels of exposure are required to induce new cases of asthma in children. This report estimates that previously asymptomatic children exposed to ETS from mothers who smoke at least 10 cigarettes per day will exhibit a probable range of 8,000 to 26,000 new cases of asthma annually. The confidence in this range is medium and is dependent on the conclusion that ETS is a risk factor for asthma induction.

4. Passive smoking has subtle but significant effects on the respiratory health of nonsmoking adults, including coughing, phlegm, chest discomfort, and reduced lung function.

This report also has reviewed data on the relationship of maternal smoking and sudden infant death syndrome (SIDS), which is thought to involve some unknown respiratory pathogenesis. The report concludes that while there is strong evidence that infants whose mothers smoke are at an increased risk of dying from SIDS, available studies do not allow us to differentiate whether and to what extent this increase is related to in utero versus postnatal exposure to tobacco smoke products. Consequently, at this time this report is unable to assert whether or not ETS exposure by itself is a risk factor for SIDS independent of smoking during pregnancy. Postnatal exposure may potentiate effects of in utero tobacco smoke exposure, or it may not have any additional effect.

Regarding an association of parental smoking with either upper respiratory tract infections (colds and sore throats) or acute middle ear infections in children, this report finds the evidence inconclusive.

1.2.1. ETS and Lung Cancer

The Surgeon General (U.S. DHHS, 1989) estimated that smoking was responsible for more than one of every six deaths in the United States and that it accounted for about 90% of the lung cancer deaths in males and about 80% in females in 1985. Smokers, however, are not the only

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ones exposed to tobacco smoke. The sidestream smoke (SS) emitted from a smoldering cigarette between puffs (the main component of ETS) has been documented to contain many of the same carcinogenic compounds (known and suspected human and animal carcinogens) that have been identified in the mainstream smoke (MS) inhaled by smokers. Exposure concentrations of these carcinogens to passive smokers are variable but much lower than for active smokers. An excess cancer risk from passive smoking, however, is biologically plausible.

Based on the firmly established causal association of lung cancer with active smoking with a dose-response relationship down to low doses (Chapter 4), passive smoking is considered likely to affect the lung similarly. The widespread presence of ETS in both home and workplace and its absorption by nonsmokers in the general population have been well documented by air sampling and by body measurement of biomarkers such as nicotine and cotinine (Chapter 3). This raises the question of whether any direct evidence exists for the relationship between ETS exposure and lung cancer in the general population and what its implications may be for public health. This report addresses that question by reviewing and analyzing the evidence from 30 epidemiologic studies of effects from normally occurring environmental levels of ETS (Chapter 5). Because there is widespread exposure and it is difficult to construct a truly unexposed subgroup of the general population, these studies compare individuals with higher ETS exposure to those with lower exposures. Typically, female never-smokers who are married to a smoker are compared with female never-smokers who are married to a nonsmoker. Some studies also consider ETS exposure of other subjects (i.e., male never-smokers and long-term former smokers of either sex) and from other sources (e.g., workplace and home exposure during childhood), but these studies are fewer and represent fewer cases, and they are generally excluded from the analysis presented here. Use of the female never-smoker studies provides the largest, most homogeneous database for analysis to determine whether an ETS effect on lung cancer is present. This document assumes that the results for female never-smokers are generalizable to all nonsmokers.

Given that ETS exposures are at actual environmental levels and that the comparison groups are both exposed to appreciable background (i.e., nonspousal) ETS, any excess risk for lung cancer from exposure to spousal smoke would be expected to be small. Furthermore, the risk of lung cancer is relatively low in nonsmokers, and most studies have a small sample size, resulting in a very low statistical power (probability of detecting a real effect if it exists). Besides small sample size and low incremental exposures, other problems inherent in several of the studies may also limit their ability to detect a possible effect. Therefore, this document examines the data in several different ways. After downward adjustment of the relative risks for smoker

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misclassification bias, the studies are individually assessed for strength of association and exposure-response trend. Then the study results are pooled by country using statistical techniques for combining data, including both positive and nonpositive results, to increase the ability to determine whether or not there is an association between ETS and lung cancer. Finally, in addition to the previous statistical analyses that weigh the studies only by size, regardless of design and conduct, the studies are qualitatively evaluated for potential confounding, bias, and likely utility to provide information about any lung carcinogenicity of ETS. Based on these qualitative considerations, the studies are categorized into one of four tiers and then statistically analyzed successively by tier.

Results from all of the analyses described above strongly support a causal association between lung cancer and ETS exposure. The overall proportion of individual studies found to show an association between lung cancer and ETS exposure is unlikely to occur by chance ($p < 0.005$). Similarly, the proportion showing a statistically significant dose-response trend ($p < 10^{-9}$) is highly supportive of a causal association. Combined results by country showed statistically significant associations for Greece (2 studies), Hong Kong (4 studies), Japan (5 studies), and the United States (11 studies), and in that order of strength of relative risk. Pooled results of the four Western European studies (three countries) actually showed a slightly stronger association than that of the United States, but it was not statistically significant, probably due to the smaller sample size. The combined results of the Chinese studies do not show an association between ETS and lung cancer; however, two of the four Chinese studies were designed mainly to determine the lung cancer effects of high levels of other indoor air pollutants indigenous to those areas, which would obscure a smaller ETS effect. These two Chinese studies do, however, provide very strong evidence on the lung carcinogenicity of these other indoor air pollutants, which contain many of the same components as ETS. When results are combined only for the other two Chinese studies, they demonstrate a statistically significant association for ETS and lung cancer.

The relative risks for Greece and Japan of 2.00 and 1.44, respectively, are probably the best estimates, because both female smoking prevalence and nontobacco-related lung cancer risks, which tend to dilute the estimates of ETS effects, are low in these two countries. Also, for the time period for which ETS exposure was of interest, spousal smoking is considered to be a better surrogate for ETS exposure in these societies than in Western countries, where other sources of ETS exposure (work, public places, and other nonhome environments) are generally higher.

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Based on these analyses and following the U.S. EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a), EPA concludes that environmental tobacco smoke is a Group A (known human) carcinogen. This conclusion is based on a total weight-of-evidence, principally:

- Biological plausibility. ETS is taken up by the lungs, and components are distributed throughout the body. The presence of the same carcinogens in ETS and mainstream smoke, along with the established causal relationship between lung cancer and active smoking with the dose-response relationships exhibited down to low doses, make it reasonable to conclude that ETS is also a lung carcinogen.
- Supporting evidence from animal bioassays and genotoxicity experiments. The carcinogenicity of tobacco smoke has been established in lifetime inhalation studies in the hamster, intrapulmonary implantations in the rat, and skin painting in the mouse. There are no lifetime animal inhalation studies of ETS; however, the carcinogenicity of ETS condensates has been demonstrated in intrapulmonary implantations and skin painting experiments. Positive results of genotoxicity testing for both MS and ETS provide corroborative evidence for their carcinogenic potential.
- Consistency of response. All 4 of the cohort studies and 20 of the 26 case-control studies observed a higher risk of lung cancer among the female never-smokers classified as exposed to ETS. Of the 17 studies judged to be of higher utility based on study design, execution, and analysis (Appendices A and C), 15 observed higher risks, and 6 of these increases were statistically significant, despite most having low statistical power. Evaluation of the total study evidence from several perspectives leads to the conclusion that the observed association between ETS exposure and increased lung cancer occurrence is not attributable to chance.
- Broad-based evidence. These 26 case-control and 4 prospective studies provide data from 8 different countries, employ a wide variety of study designs and protocols, and are conducted by many different research teams. Results from all countries, with the possible exception of two areas of China where high levels of other indoor air lung carcinogens were present, show small to modest increases in lung cancer associated with spousal ETS exposure. No alternative explanatory variables for the observed association between ETS and lung cancer have been indicated that would be broadly applicable across studies.

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- Upward trend in dose-response. Both the largest of the cohort studies, the Japanese study of Hirayama--200 lung cancer cases, and the largest of the case-control studies, the U.S. study by Fontham and associates (1991)--420 lung cancer cases and two sets of controls, demonstrate a strong dose-related statistical association between passive smoking and lung cancer. This upward trend is well supported by the preponderance of epidemiology studies. Of the total of 17 studies in which data are classified by exposure level, 11 were statistically significant for the trend despite most having low statistical power.
- Detectable association at environmental exposure levels. Within the population of married women who are lifelong nonsmokers, the excess lung cancer risk from exposure to their smoking husbands' ETS is large enough to be observed. Carcinogenic responses are usually detectable only in high-exposure circumstances, such as occupational settings, or in experimental animals receiving very high doses. In addition, effects are harder to observe when there is substantial background exposure in the comparison groups, as is the case here.
- Effects remain after adjustment for potential bias. Current and ex-smokers may be misreported as never-smokers, thus inflating the apparent cancer risk for ETS exposure. The evidence remains statistically significant and conclusive, however, after adjustments for smoker misclassification. For the United States, the summary estimate of relative risk from nine case-control plus two cohort studies is 1.19 (90% confidence interval [C.I.] = 1.04-1.35) after adjustment for misclassification ($p < 0.05$). For Greece, 2.00 (1.42, 2.83), Hong Kong, 1.61 (1.25, 2.06) and Japan, 1.44 (1.13, 1.85), the estimated relative risks are higher than those of the United States and more highly significant after adjusting for the potential bias.
- Confounding cannot explain the association. The broad-based evidence for an association found by independent investigators across several countries, as well as the positive dose-response trends observed in most of the studies that analyzed for them, make any single confounder highly unlikely as an explanation for the results. In addition, this report examined potential confounding factors (history of lung disease, home heat sources, diet, occupation) and concluded that none of these factors could account for the observed association between lung cancer and ETS.

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The individual risk of lung cancer from exposure to ETS does not have to be very large to translate into a significant health hazard to the U.S. population because of the large number of smokers and the widespread presence of ETS. Current smokers comprise approximately 26% of the U.S. adult population and consume more than one-half trillion cigarettes annually (1.5 packs per day, on average), causing nearly universal exposure to at least some ETS. As a biomarker of tobacco smoke uptake, cotinine, a metabolite of the tobacco-specific compound nicotine, is detectable in the blood, saliva, and urine of persons recently exposed to tobacco smoke. Cotinine has typically been detected in 50% to 75% of reported nonsmokers tested (50% equates to 63 million U.S. nonsmokers of age 18 or above).

The best estimate of approximately 3,000 lung cancer deaths per year in U.S. nonsmokers age 35 and over attributable to ETS (Chapter 6) is based on data pooled from all 11 U.S. epidemiologic studies of never-smoking women married to smoking spouses. Use of U.S. studies should increase the confidence in these estimates. Some mathematical modeling is required to adjust for expected bias from misclassification of smoking status and to account for ETS exposure from sources other than spousal smoking. Assumptions are also needed to relate responses in female never-smokers to those in male never-smokers and ex-smokers of both sexes, and to estimate the proportion of the nonsmoking population exposed to various levels of ETS. Overall, however, the assumptions necessary for estimating risk add far less uncertainty than other EPA quantitative assessments. This is because for ETS the extrapolation is based on a large database of human studies, all at levels actually expected to be encountered by much of the U.S. population.

The components of the 3,000 lung cancer deaths figure include approximately 1,500 female never-smokers, 500 male never-smokers, and 1,000 former smokers of both sexes. More females are estimated to be affected because there are more female than male nonsmokers. These component estimates have varying degrees of confidence; the estimate of 1,500 deaths for female never-smokers has the highest confidence because of the extensive database. The estimate of 500 for male never-smokers is less certain because it is based on the female never-smoker response and is thought to be low because males are generally subject to higher background ETS exposures than females. Adjustment for this higher background exposure would lead to higher risk estimates. The estimate of 1,000 lung cancer deaths for former smokers of both sexes is considered to have the lowest confidence, and the assumptions included are thought to make the estimate low as well.

Workplace ETS levels are generally comparable to home ETS levels, and studies using body cotinine measures as biomarkers demonstrate that nonhome exposures to ETS are often greater

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than exposure from spousal smoking. Thus, this report presents an alternative breakdown of the estimated 3,000 ETS-attributable lung cancer deaths between spousal and nonhome exposures. By extension of the results from spousal smoking studies, coupled with biological measurements of exposure, more lung cancer deaths are estimated to be attributable to ETS from combined nonhome exposures - 2,200 of both sexes - than from spousal exposure - 800 of both sexes. This home-versus-other-sources partitioning depends on current exposure estimates that may or may not be applicable to the exposure period of interest. Thus, this breakdown contains this element of uncertainty in addition to those discussed above with respect to the previous breakdown.

Other estimates of annual U.S. nonsmoker lung cancer deaths attributable to ETS developed in this document give a range of 2,500 to 3,300. These other estimates use both mortality and cotinine exposure data from the largest and best-designed U.S. study (Fontham et al., 1991). Relatively small differences in cotinine ratios, as measures of exposure from spousal smoking, can result in substantial variability in population risk estimates. The range suggested above provides an estimation of the uncertainty in these estimates. Overall, however, considering the multitude, consistency, and quality of all these studies, the weight-of-evidence conclusion that ETS is a known human lung carcinogen, and the limited amount of extrapolation necessary, the confidence in the estimate of approximately 3,000 lung cancer deaths is medium to high.

1.2.2. ETS and Noncancer Respiratory Disorders

Exposure to ETS from parental smoking has been previously linked with increased respiratory disorders in children, particularly in infants. Several studies have confirmed the exposure and uptake of ETS in children by assaying saliva, serum, or urine for cotinine. These cotinine concentrations were highly correlated with smoking (especially by the mother) in the child's presence. Nine million to twelve million American children under 5 years of age, or one-half to two-thirds of all children in this age group, may be exposed to cigarette smoke in the home (American Academy of Pediatrics, 1986).

With regard to the noncancer respiratory effects of passive smoking, this report focuses on epidemiologic evidence appearing since the two major reports of 1986 (NRC and U.S. DHHS) that bears on the potential association of parental smoking with detrimental respiratory effects in their children. These effects include symptoms of respiratory irritation (cough, sputum, or wheeze); acute diseases of the lower respiratory tract (pneumonia, bronchitis, and bronchiolitis); acute middle ear infections and indications of chronic middle ear infections (predominantly middle ear effusion); reduced lung function (from forced expiratory volume and flow-rate measurements);

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incidence and prevalence of asthma and exacerbation of symptoms in asthmatics; and acute upper respiratory tract infections (colds and sore throats). The more than 50 recently published studies reviewed here essentially corroborate the previous conclusions of the NRC and Surgeon General regarding respiratory symptoms, respiratory illnesses, and pulmonary function, and they strengthen support for those conclusions by the additional weight-of-evidence (Chapter 7). For example, new data on middle ear effusion strengthen previous evidence to warrant the stronger conclusion in this report of a causal association with parental smoking. Furthermore, recent studies establish associations between parental smoking and increased incidence of childhood asthma. Additional research also supports the hypotheses that in utero exposure to mother's smoke and postnatal exposure to ETS alter lung function and structure, increase bronchial responsiveness, and enhance the process of allergic sensitization, changes that are known to predispose children to early respiratory illness. Early respiratory illness can lead to long-term pulmonary effects (reduced lung function and increased risk of chronic obstructive lung disease).

This document also summarizes the evidence for an association between parental smoking and SIDS, which was not addressed in the 1986 NRC or Surgeon General reports. SIDS is the most common cause of death in infants ages 1 month to 1 year. The cause (or causes) of SIDS is unknown; however, it is widely believed that some form of respiratory pathogenesis is generally involved. The current evidence strongly suggests that infants whose mothers smoke are at an increased risk of dying of SIDS, independent of other known risk factors for SIDS, including low birthweight and low gestational age, which are specifically associated with active smoking during pregnancy. However, available studies do not allow this report to conclude whether that increased risk is related to in utero versus postnatal exposure to tobacco smoke products, or to both.

The 1986 NRC and Surgeon General reports conclude that both the prevalence of respiratory symptoms of irritation and the incidence of lower respiratory tract infections are higher in children of smoking parents. In the 18 studies of respiratory symptoms subsequent to the 2 reports, increased symptoms (cough, phlegm, and wheezing) were observed in a range of ages from birth to midteens, particularly in infants and preschool children. In addition to the studies on symptoms of respiratory irritation, nine new studies have addressed the topic of parental smoking and acute lower respiratory tract illness in children, and eight have reported statistically significant associations. The cumulative evidence indicates strongly that parental smoking, especially the mother's, causes an increased incidence of respiratory illnesses from birth up to the first 18 months to 3 years of life, particularly for bronchitis, bronchiolitis, and

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pneumonia. Overall, the evidence confirms the previous conclusions of the NRC and Surgeon General.

Recent studies also solidify the evidence for the conclusion of a causal association between parental smoking and increased middle ear effusion in young children. Middle ear effusion is the most common reason for hospitalization of young children for an operation.

At the time of the Surgeon General's report on passive smoking (U.S. DHHS, 1986), data were sufficient only to conclude that maternal smoking may influence the severity of asthma in children. The recent studies reviewed here strengthen and confirm these exacerbation effects. In addition, the new evidence is conclusive that ETS exposure increases the number of episodes of asthma in children who already have the disease. It is also suggestive that ETS exposure increases the number of new cases of asthma in children who have not previously exhibited symptoms, although the results are statistically significant only with children whose mothers smoke 10 or more cigarettes per day. While the evidence for new cases of asthma itself is not conclusive of a causal association, the consistent strong associations of ETS with both increased frequency and severity of the asthmatic symptoms and the established ETS effects on both the immune system and airway hyperresponsiveness lead to the conclusion that ETS is a risk factor for induction of asthma in previously asymptomatic children.

Regarding the effects of passive smoking on lung function in children, the 1986 Surgeon General and NRC reports both conclude that children of parents who smoke have small decreases in tests of pulmonary output function of both the larger and smaller air passages when compared with the children of nonsmokers. As noted in the NRC report, if ETS exposure is the cause of the observed decrease in lung function, the effect could be due to the direct action of agents in ETS or an indirect consequence of increased occurrence of acute respiratory illness related to ETS.

Results from eight studies on ETS and lung function in children that have appeared since those reports add some additional confirmatory evidence suggesting a causal rather than an indirect relationship. For the population as a whole, the reductions are small relative to the interindividual variability of each lung function parameter. However, groups of particularly susceptible or heavily exposed subjects have shown larger decrements. The studies reviewed suggest that a continuum of exposures to tobacco products starting in fetal life may contribute to the decrements in lung function found in older children. Exposure to tobacco smoke products inhaled by the mother during pregnancy may contribute significantly to these changes, but there is strong evidence indicating that postnatal exposure to ETS is an important part of the causal pathway.

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With respect to lung function effects in adults exposed to ETS, the 1986 NRC and Surgeon General reports found the data at that time inconclusive, due to high interindividual variability and the existence of a large number of other risk factors, but compatible with subtle deficits in lung function. Recent studies confirm the association of passive smoking with small reductions in lung function. Furthermore, new evidence also has emerged suggesting a subtle association between exposure to ETS and increased respiratory symptoms in adults.

There is some evidence suggesting that the incidence of acute upper respiratory tract illnesses and acute middle ear infections may be more common in children exposed to ETS. However, several studies failed to find any effect. In addition, the possible role of confounding factors, the lack of studies showing clear dose-response relationships, and the absence of a plausible biological mechanism preclude more definitive conclusions.

In reviewing the available evidence indicating an association (or lack thereof) between ETS exposure and the different noncancer respiratory disorders analyzed in this report, the possible role of several potential confounding factors was considered. These include other indoor air pollutants; socioeconomic status; effect of parental symptoms; and characteristics of the exposed child, such as low birthweight or active smoking. No single or combined confounding factors can explain the observed respiratory effects of passive smoking in children.

For diseases for which ETS has been either causally associated (lower respiratory tract infections) or indicated as a risk factor (asthma cases in previously asymptomatic children), estimates of population attributable risk can be calculated. A population risk assessment (Chapter 8) provides a probable range of estimates that 8,000 to 26,000 cases of childhood asthma per year are attributable to ETS exposure from mothers who smoke 10 or more cigarettes per day. The confidence in this range of estimates is medium and is dependent on the suggestive evidence of the database. While the data show an effect only for children of these heavily smoking mothers, additional cases due to lesser ETS exposure are also a possibility. If the effect of this lesser exposure is considered, the range of estimates of new cases presented above increases to 13,000 to 60,000. Furthermore, this report estimates that the additional public health impact of ETS on asthmatic children includes over 200,000 children whose symptoms are significantly aggravated and as many as 1,000,000 children who are affected to some degree.

This report estimates that ETS exposure contributes 150,000 to 300,000 cases annually of lower respiratory tract illness in infants and children younger than 18 months of age and that 7,500 to 15,000 of these will require hospitalization. The strong evidence linking ETS exposure to increased incidence of bronchitis, bronchiolitis, and pneumonia in young children gives these

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estimates a high degree of confidence. There is also evidence suggesting a smaller ETS effect on children between ages 18 months and 3 years, but no additional estimates have been computed for this age group. Whether or not these illnesses result in death has not been addressed here.

In the United States, more than 5,000 infants die of SIDS annually. It is the major cause of death in infants between the ages of 1 month and 1 year and the linkage with maternal smoking is well established. The Surgeon General and World Health Organization estimate that more than 700 U.S. infant deaths per year from SIDS are attributable to maternal smoking (U.S. CDC, 1991a). However, this report concludes that at present there is not enough direct evidence supporting the contribution of ETS exposure to declare it a risk factor or to estimate its population impact on SIDS.

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